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Nanomaterials for treating cardiovascular diseases: A review

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ABSTRACT

Nanomaterials such as nanostructured surfaces, nanoparticles, and nanocomposites represent new viable sources for future therapeutics for cardiovascular diseases. The special properties of nanomaterials such as their intrinsic physiochemical properties, surface energy and surface topographies could actively enhance desirable cellular responses within the cardiovascular system, projecting a growing potential for clinical translation. Recent progress on nanomaterials opened up new opportunities for treating cardiovascular diseases. Successful translation of nanomaterials into cardiovascular applications requires a comprehensive understanding of both nanomaterials and biomedicine, and, thus, it is critical to stress current advancements on both sides. In this review, the authors introduced crucial fabrication techniques for promising nanomaterials for cardiovascular applications. This review highlighted the key elements to consider for their fabrication, properties and applications. The important concerns relevant to cardiovascular nanomaterials, such as cellular responses to nanomaterials and the toxicity of nanomaterials, are also discussed. This review provided an overview of necessary knowledge and key concerns on nanomaterials specific for treating cardiovascular diseases, from the perspectives of both material science and biomedicine.

1. Introduction

Cardiovascular diseases (CVDs) are one of the major causes of human death worldwide and responsible for more than 17.7 million deaths in 2015, according to world health organization [1]. CVDs are also a major health concern in the United States of America. It has affected the lives of 85.6 million Americans [2]. In 2011, CVDs led to more than 596 thousand deaths and was the top cause of death in the United States of America [3]. Due to the high incidence of CVDs, the need for developing effective treatments for CVDs is urgent; and motivates the research and development of biomaterials for cardiovascular applications. The application of cardiovascular biomaterials has gained great success in the past. For example, coronary artery stent, a device mostly made of medical-grade metallic alloys, significantly improved the treatments for heart attack by providing mechanical support to the narrowed vessels. In the year of 2007, about 560,000 surgeries for placing coronary arteries stents were performed in the U.S. [4]. Such examples indicate a few of many successful biomaterials. A broad range of applications in CVDs is now investigated and translated within the field of cardiovascular engineering and regenerative medicine, and much of their success is heavily rooted in advancements in biomaterials science. Such applications include, but are not limit to the targeted drug delivery, CVD diagnosis, and the repair and regeneration of the cardiac tissues. It is clear that biomaterials are at the core of further progress for CVD treatments.

Nanomaterials presented unprecedented opportunities for overcoming the limits of conventional biomaterials. The development of nanostructured surfaces, nanoparticles, and nanocomposites could greatly improve the performance of conventional biomaterials [5,6]. Moreover, the progress in the field of nanomaterials can inspire a number of new therapeutic strategies which could revolutionize the treatment of CVDs. Nanomaterials have size features ranging from the protein level (a few nanometers) to cellular level (sub-micron size), mimicking the extracellular matrix and microenvironment for the cells and hierarchical tissue structures [5–8]. On the other hand, nanomaterials have significantly different physicochemical properties compared with conventional

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materials. Their high surface to volume ratio, high surface energy and activity, as well as altered wettability could profoundly influence the adhesion of proteins and the activities of cells [5,6,9–13]. Moreover, nanomaterials can achieve certain therapeutic functions that would be rather difficult to achieve using conventional biomaterials. Nanoparticles, for instance, can act as drug carrier that can travel through the endothelium of blood vessels. If properly functionalized, they can also enter cells via the internalization processes and then deliver the pre-loaded drugs or genes. In addition, some nanoparticles can be used as contrast agents for magnetic resonance imaging (MRI) and many other bioimaging technologies. None of these missions could be easily accomplished using conventional materials.

Nanomaterials are particularly useful in cardiovascular applications, where they demonstrated potentials across several applications. Firstly, controlling topographical cues of nanostructured surfaces can selectively direct cell activities [14–20]. This capability of cellular guidance is very useful in certain cardiovascular applications where promoting functions of some type of cells while suppressing activities of another type of cells are preferred. For example, the implantation of coronary stents usually leads to neointimal hyperplasia [21,22]. Promoting adhesion and functions of endothelial cells while suppressing smooth muscle cells may facilitate healing process and endothelial layer formation while inhibiting excessive neointimal formation [21,22]; therefore, selective cell stimulation could potentially lead to a better and faster endothelialization. In addition to nanoscale surface features, nanoparticles can serve as a platform carrying multiple functional groups and provide exciting opportunities for potential cardiovascular applications. Such nano-platform can integrate the functions of targeting, imaging and therapeutics in one particle. Moreover, recently-developed nanocomposites can use nanoparticles as a key component to greatly enhance the mechanical and biological performances of current cardiovascular implants and devices [23–26]. Integrating nanoscale components of different chemical compositions, distinct size, morphologies and functions into a matrix material, for example, polymers is a controllable and reliable approach to obtain complementary properties desirable for medical needs.

Nanomaterials are the potential game-changer in many aspects of treatments for CVDs. Breakthroughs in nanomaterials could greatly enhance the efficacy of treatments that use biomaterials and could even provide innovative therapies. Much progress has been made in the past decades to apply nanomaterials and nanotechnologies to the field of CVD treatments, but their full potential remains largely unexplored considering that nanoscience has been continuing to advance swiftly [27–29]. This review article intends to bridge the needs in CVD treatments with the innovations of nanomaterials and provides an overview on recent key development, considering comprehensive reviews on current progress of nanomaterials with specific focuses on CVD treatments are missing in existing literatures. On this ground, this review will introduce three categories of mostly-studied cardiovascular nanomaterials: nanostructured surfaces on biomaterial, nanoparticles and nanocomposites. We will discuss the fabrication for these nanostructures and relevant principles from the material science perspective, and their applications with an emphasis in the treatment of CVDs.

2. Nanostructured surfaces for cardiovascular applications

Creating nanofeatures on surface is a promising approach to improve biological performances of medical implants to realize certain therapeutic objectives. The surface of biomaterials provides an interface between human body and implants. Nanofeatures on materials surface directly interact with proteins and biological molecules inside the body because of similar dimension, and thus influence the biological responses at the cellular and tissue level. The advances in nanofabrication and nanotechnologies enabled the precise creation of various nanostructures on materials surface for therapeutic devices, such as reservoirs for cells [14–16] or drugs [30]. The specially modified nano-surfaces, therefore, could potentially induce desirable biological responses to the implants. Nanostructures have unique surface and physicochemical properties that can greatly improve the biological performance of biomaterials; such properties include surface energy, surface area to volume ratio, surface roughness, wettability, and reactivity. The nanostructured surfaces can be categorized into “random nanostructures” and “well-ordered nanostructures”. The ordered surface nanostructures also possess unique surface energy, surface area, roughness, wettability and other physicochemical properties similar to the random nanostructures. However, the ordered surface nanostructures have additional influences on cell activities which cannot be achieved by any random nanostructures, *e.g.* improving cell alignment based on the principle of contact guidance [31].

Introducing nanostructured surface to conventional materials that have been used in FDA-approved medical implants and devices is also considered to be less risky while keeping their desired therapeutic functions, from the regulatory point of view such as FDA, when compared with a brand new material that has never been used in approved implants. The development of new materials and drugs usually involves high risks and requires massive efforts toward FDA approval. For example, current drug-eluting stents face the late complications because of the side effects of anti-inflammatory and anti-proliferative drugs which delay endothelialization [22,32–34]. In this case, whether nanopatterning on a well-known safe material (approved by FDA for medical uses) could potentially replace the anti-proliferative drugs or not surely deserves intensive investigations.

2.1. Physicochemical properties of nanostructured surfaces

It is well known that nanomaterials have a significantly increased surface area to volume ratio as well as surface energy when compared with conventional materials. For nanostructured surface and nanoparticles, for example, the surface area will increase in several orders of magnitude when the size feature of unit nanostructure or particle reduces from macro-size level down to nano-size level while the bulk mass and chemical composition remain unchanged. The surface energy will also increase as a consequence of greater surface area and more broken bonds at nano-surfaces. The presence of nanofeatures could also significantly increase nano-scale roughness.

Wettability is another important property that may change mainly by nanostructured surface. Wettability, or hydrophilicity/hydrophobicity, is usually quantified by water contact angle measurements. Significantly increased surface roughness could have complicated effects on surface wettability. Reports on some materials suggested that water contact angle usually increases on rougher surfaces in a certain range, but for highly hydrophilic surface, a rougher surface at the nano-scale could lead to lower contact angle [35,36]. Creating nano-scale structures on hydrophobic materials could make them more hydrophobic, while creating nano-scale features on hydrophilic materials could make them more hydrophilic.

2.2. Fabrication approaches for nanostructured surfaces

Fabrication approaches to engineer nano-to submicron-structures on materials surface have been developed and studied for

many years, but most methods have been focused on or originated from electronic materials. In the field of biomaterials, nanostructured surface is an emerging area that has attracted increasing attention in recent years [15,20,37–42]. In the early years of studying nanostructured surface for biomedical applications, chemical etching was utilized as an easy method to produced random nanostructures on material surface [43]. In terms of generating a more delicate, well-defined and ordered structure, microfabrication and nanofabrication techniques originally established for electronic applications presented great potentials. Representative nanofabrication approaches, for example, nanolithography, laser writing, 3D printing, electrochemical approaches, will be reviewed in this section, as summarized in Table 1.

2.2.1. Chemical etching

Chemical etching is a simple but effective method to create nano-sized surface features on polymeric or metallic materials. For example, Tapha et al. [44] reported etching approach to obtain surface nanostructures. Specifically, sodium hydroxide (NaOH) was used to etch poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) to produce nanostructures on the surface, as shown in Fig. 1a [44]; nitric acid (HNO_3) was used to etch poly(-ether urethane) (PU) to obtain nanostructured surface [44]. The etching process utilizes the hydrolysis of ester bond in the polymers [44]. The presence of acid or alkaline accelerated the etching process. In addition, NaOH etching was also used on magnesium [45], a biodegradable metal promising for cardiovascular applications. The major advantage of this approach is easy and fast sample preparation, as well as its potential for scaling up to industrial production. Despite that the chemical etching approach usually generates a random topology and morphology, it can certainly achieve a high surface roughness, a high surface energy, a chemically-modified surface, and a drastically altered wettability in a relatively easy and affordable way [44,45].

2.2.2. Photolithography

Photolithography is a well-established approach for nanofabrication. Photolithography utilizes the photochemical reaction of a photoresist layer, that is, a layer of light-sensitive material. Specifically, an incident light is applied onto a photoresist layer with a mask shielding in between. The solubility of certain area where the photoresist is exposed to the incident light will increase or decrease due to the photochemical reaction. A following development process will leach out the more soluble area of the photoresist while keeping the less soluble area. The subsequent etching on the target materials beneath the photoresist layer could copy the same nanopattern from the photoresist layer. Unfortunately, photolithography is relatively difficult to be applied to polymers because it is rather difficult to control the etching process of polymers. This could limit the use of photolithography for cardiovascular applications where polymers often play important roles in drug delivery, cardiac patch, scaffolds and many other implantable devices.

The field of photolithography has progressed significantly in the past decades due to the demand of semiconductor industries. The incident light used for photolithography evolves from the originally ultraviolet (UV) ray to extreme ultraviolet ray [46,47] and x-ray [48–50]. Such progress has pushed photolithography to a high level of fidelity, resolution and controllability even in the scale of tens of nanometer. For example, Fig. 1b [47] shows a well-organized nano-island array which has a 50 nm periodic distance, which was fabricated by extreme ultraviolet interference lithography. For biomedical applications, some efforts were made to fabricate microscopic features on polymers [51–53], but the fabrication of nanostructures on polymeric surfaces remains a challenge for photolithography. Fortunately, photolithography on the surface of metals and alloys is very promising for cardiovascular applications due to its high controllability and versatility, especially for those alloy systems that attracted broad interests for biomedical applications, *e.g.* Ti alloys, Mg alloys and Zn alloys.

2.2.3. Capillary force lithography

Capillary force lithography (CFL) is a typical mold-based nanofabrication approach. It has a great flexibility, which allows for its application on various biopolymers. CFL is a simple and affordable patterning approach which can be applied to large areas [40,54]. The fabrication process of CFL was thoroughly reviewed elsewhere [55]. Briefly, CFL utilizes the capillary force between the polymer and a nanopatterned elastomeric mold, *e.g.* polydimethylsiloxane (PDMS), to rise the polymer up toward the mold [55]. The capillary rise could occur after the polymer was softened by heating up to above its glass transition temperature T_g [55]. CFL can be applied to either hydrophilic or hydrophobic polymers [55,56]. For example, Yang et al. [40] fabricated a nano-to sub-micron parallel groove patterns on PLGA film using CFL, as shown in Fig. 1c [40]. The parallel groove and ridge were both 800 nm wide; and the ridge height was 600 nm [40]. The patterns successfully guided muscle cell orientation, changed morphology (elongation) and influenced cellular maturation [40]. Interestingly, the nanopatterned patch seeded with the nanopattern-tuned muscle cells showed great potential to facilitate myogenesis [40]. Liliensiek et al. [42] used CFL to create both parallel groove-and-ridge patterns and hole patterns of micron to sub-micron size on silicon, and found that the groove-and-ridge pattern could influence cell morphology, proliferation, direction and the rate of cell migration, while the hole pattern could influence cell proliferation and the rate of cell migration. Specific results of Liliensiek's experimental work were seen in the alignment and orientation of the different cell types [42], including human dermal microvascular endothelial cells (HmVEC-d), human saphenous vein endothelial cells (HSaVEC-c), human umbilical vein endothelial cells (HUVEC), and human aortic endothelial cells (HAEC) [42]. The cell types were grown on the groove patterns with

Table 1
Summary of representative fabrication approaches for nanostructured surfaces.

Fabrication Approaches	Applicable Materials	Examplary Nanostructures	Material Versatility	Morphology Versatility	References
Chemical Etching	Metals, Polymers.	Rough Surface	High	Low versatility, Random morphology, Low controllability.	[44,45]
Photolithography	Metals, Ceramics.	Parallel Groove, Dot array.	Low	High versatility, Ordered morphology, High controllability.	[46–53,134]
Capillary Force Lithography	Polymers	Parallel Grooves, Nanowire.	Medium (applied to most polymers)	High versatility, Ordered morphology, High controllability.	[40,42,54–56,135]
Direct Writing	Polymers, Ceramics, Metals.	Parallel, Grooves, Nanowire.	Medium	High versatility, Ordered morphology, Medium controllability.	[57–60]
Anodization	Metals	Nanopores, Nanotubes.	Very low (mostly TiO_2)	Low versatility, Random or ordered morphologies, Medium controllability.	[14–16,30,67,69]

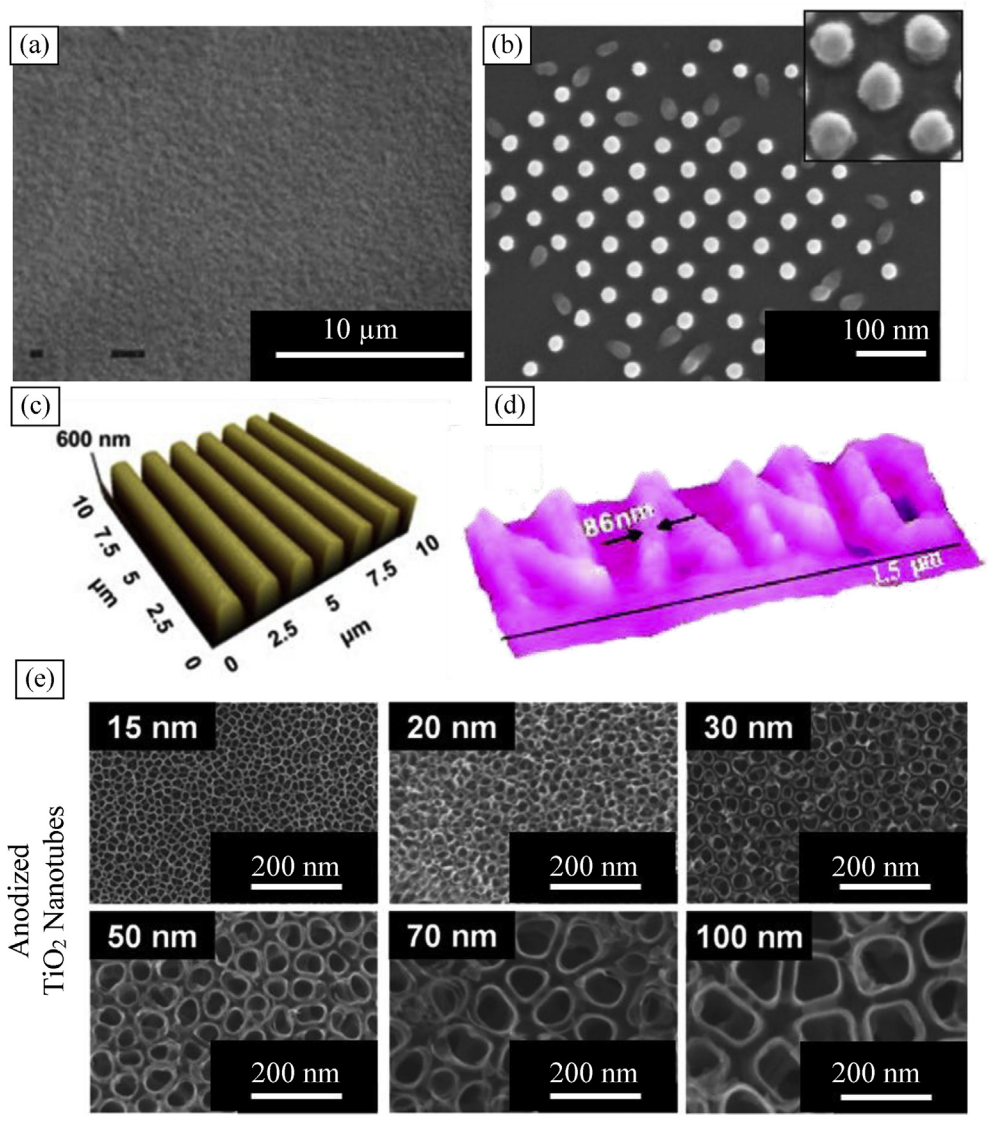

Fig. 1. Morphologies of representative nanostructured surfaces. (a) Nanorough poly-ether-urethane surface fabricated by alkaline chemical etching using NaOH (adapted from Ref. [44] with permission by John Wiley and Sons). (b) 50 nm-periodic array of nanoscale Co/Pd-coated SiO_x islands fabricated by exteme ultraviolet inteference lithography (Reprinted from Ref. [47] (Luo F, Heyderman L, Solak H, Thomson T, Best M, *Nanoscale perpendicular magnetic island arrays fabricated by extreme ultraviolet interference lithography*. Applied Physics Letters 2008; 92:102505.) with the permission of AIP publishing. (c) Nanopattened parallel grooves on the surface of PLGA (50:50) with 800 nm ridge width and 800 nm groove width, fabricated by capillary force lithography [40] (reprinted from Biomaterials, 2014. **35**(5), Yang HS, Ieronimakis N, Tsui JH, Kim HN, Suh K-Y, Reyes M et al., *Nanopatterned muscle cell patches for enhanced myogenesis and dystrophin expression in a mouse model of muscular dystrophy*. p. 1478–1486. Copyright (2017), with permission from Elsevier). (d) 3D image of nanopatterned "NANO" made of cross-linked carbozole drawn on a film of precursoe polycarbozole, imaged using an atomic force microscope. (adapted and reprinted with permission from Ref. [58] (Jegadesan S, Sindhu S, Advincula RC, Valiyaveettil S, *Direct electrochemical nanopatterning of polycarbazole monomer and precursor polymer films: ambient formation of thermally stable conducting nanopatterns.* Langmuir, 2006. **22**(2): p. 780–786.). Copyright (2017) American Chemical Society. (e) Anodized TiO_2 nanotubes with six different pore sizes from 15 nm to 100 nm (adapted and reprinted with permission from Ref. [14] (Park J, Bauer S, von der Mark K, Schmuki P, *Nanosize and vitality: TiO_2 nanotube diameter directs cell fate*. Nano letters, 2007. **7**(6): p. 1686–1691.). Copyright (2017) American Chemical Society.). Scale bar = 10 μm for (a), 100 nm for (b), 1.5 μm for (d) and 200 nm for (e).

pitch size from 400 nm to 4000 nm, and greatest orientation and alignment of these cell types occurred on groove patterns with pitch size greater than 800 nm [42]. Interestingly, this study also found that the suppressing effect of HUVEC adhesion was possible for smaller grooves (pitch size < 800 nm), which suggested that the groove size should be carefully selected for controlling cell activities [42]. In summary, CFL can be used to fabricate micro-to nano-topographies for a variety of polymeric biomaterials. As an affordable and versatile approach effective on a large area, CFL should be considered as an efficient tool for making research models for studying nanopatterned biomaterials and scalable industrial productions for nanopatterned biomaterials or medical devices.

2.2.4. Direct writing

Direct writing is an emerging approach of free-form fabrication technology similar to rapid prototyping and additive manufacturing. However, in direct writing. The substrate is usually considered as a part of final product, which is different from rapid prototyping, or 3D-printing [57]. One of the fascinating features of direct writing is that it eliminates the need for substrate removal. Many applications do not require the substrates to be removed, such as surface modification where substrates are still necessary. It also avoids the use of supporting materials, which is time-consuming to remove. Typically, direct writing utilizes droplet, energy beam, flow fluid or tip pen for patterning materials [57].

Various materials, including metals, ceramics, polymers and even living cells, could be printed via this technology [57]. Direct writing does not require a mask or mold, which further simplifies the process of fabrication [57]. Direct writing method is also widely open to do-it-yourself optimization based on specific applications. The key principles for a successful direct writing include (1) the choice of energy beam or tip pen to write features in nanoscale size with high precision and stability, and (2) transformation from directly-written drop to physically solid nanostructures. For example, Subbiah et al. [58] used a voltage-biased AFM (atomic force microscopy) tip to successfully write the word "NANO" with line features smaller than 100 nm (Fig. 1d [58]). The materials were transferred from the tip to the surface of substrates by voltage-induced polymerization. In contrast, Maynor et al. [59] utilized a electrochemical AFM dip-pen to successfully draw 30 nm poly-EDOT nanowires. In this example, the transferring of liquid monomer to the surface of substrate relied on the chemical process occurring at the tip. In addition, Lai et al. [60] used electron beam to obtain 70–280 nm Cu nanowires. The electron beam induced the Cu deposition on the surface of the substrate. In these examples, the choice of the "pen", either a physical dip-pen or electron beam, is very critical to the quality of the written structures. In addition to the "pen", the appropriate chemical process which transforms the drop into solid nanostructures is also of great importance. In the above studies [58,59], monomers were first printed, and polymerization occurred either spontaneously [59] or subsequently [58]. For polymers, polymerization provides an excellent chemical process to directly write nanostructures. For metals, reduction reaction could be used to directly write nanostructures. Lai et al. [60] used electron beam to induce the reduction of Cu^{2+} into Cu solid in the solution of $CuSO_4$, which produced Cu nanowires. The design of chemical or physical process that results in final solid nanostructures should be taken into thorough consideration to achieve a successful direct writing fabrication.

The applications of direct writing could potentially expand to many aspects of cardiovascular engineering. First, direct writing can fabricate diverse microfluidic systems that mimic microvascular networks in the body [61,62], which was thoroughly reviewed previously [63]. Second, direct writing is a promising technique to fabricate polymer scaffolds for biomedical and tissue engineering applications [64,65]. The future direction of direct printing is very likely to be printing cells directly. For example, human cardiac progenitor cells were successfully printed to form a construct for treating cardiac tissue damage [66]. These successful applications of direct writing open a window to new structures for cardiovascular applications.

2.2.5. Anodization

Anodization is an electrochemical approach used to generate nanopores, nanotubes and other nano-sized features on metallic surfaces. For example, Lei et al. anodized Mg in a potassium hydroxide (KOH) solution to obtain nano-scale porous structures [67]. The most successful creation of anodized nanotubes is on titanium (Ti) alloys and aluminum (Al) alloys; and Ti alloys are more suitable for biomedical applications than Al due to the lower toxicity than Al. Synthesis and applications of TiO_2 nanotubes have been thoroughly reviewed previously [68,69]. The anodic growth of TiO_2 is a highly-controllable process, which allows to fabricate well-defined nanotubes with different pore size. For example, Fig. 1e [14] showed a successful anodization of TiO_2 nanotubes with pore sizes ranging from 15 nm to 100 nm. Anodized TiO_2 nanotubes on Ti alloys provide multiple functions for biomedical applications. For example, these nanotubes could be used for directing cell behaviors [14–16] or used as drug reservoir for delivering drugs [30]. Interestingly, anodized Mg nanotubes were rarely reported. The difficulties in fabricating MgO nanotubes on Mg surface partially come from the fact that it is difficult to form a compact MgO oxide layer Mg, and formation of a compact oxide layer is indispensable for the anodic growth of nanotubes [69]. Additionally, it is important for the anodic growth of nanotubes that transition from metal to metal oxide during anodization should undergo a volume expansion [69], which is not likely to occur on Mg. Interestingly, in an attempt by Turhan et al. in 2010 [70], mixed morphologies of fluorine (F)-containing MgO nanopores and nanotubes on the surface of Mg alloy were produced using anodization in a non-aqueous electrolyte, *i.e.* hydrofluoric acid (HF)-added ethylene glycol. This work is the closest one to ordered nanotubes on anodized Mg alloy to date, but it still suggested the big challenge to create well-defined, well-organized and self-ordered nanotubes with high-fidelity and high purity on Mg surface using anodization process. Lack of a dense oxide layer and low volume expansion during anodization must be addressed in order to produce desirable nanotubes on Mg, and the use of new electrolyte and different Mg alloy system may provide some hope for future studies.

2.3. Nanostructured surface and cell behaviors

In the body, cells naturally interact with its surrounding environment, *i.e.* extracellular matrix. The chemical composition, physicochemical properties and topographical cues of the surrounding environment all play very important roles in cell-material interactions. For nanostructured surface, their various characteristics can mediate proteins and affect cell adhesion, proliferation, differentiation and phenotype [5,6]. These characteristics include surface energy, surface area, surface roughness, wettability, electrical charge, topography, morphology, chemical composition and mechanical properties. For example, a nanorough surface was found to attract more vitronectin on surface and resulted in greater cell adhesion [71]. When it comes to specific applications, such effects should be considered thoroughly and properly. For example, enhanced adhesion of certain cells could be a favorable or an adverse event depending on the applications. For cardiovascular stents, increased adhesion of endothelial cells is desired for fast endothelialization, while promoted adhesion and growth of smooth muscle cells may lead to excessive formation of neointima that could block vessel lumen [21,22]. All these factors should be taken into consideration when designing nanostructures for cardiovascular applications.

In addition to altered physicochemical properties by nanostructures, topography itself has been known to have certain biological effects. Many studies have been carried out to reveal the biological influences of topographies on different materials. For example, Pan et al. [17] reported that Pt-coated 50 nm nanodot array on Si wafer greatly increased the spreading area and proliferation of cardiomyoblasts as compared with flat Si substrate, even though stiff Si wafers may not be desirable substrates for cardiovascular applications. Clearly, investigation of nanostructures directly patterned on clinically relevant biomaterials would be more useful for clinical applications. For example, Cipriano el al. [31] investigated parallel groove patterns on Ti substrates, and found that adhesion of bone marrow stromal cell greatly increased on the patterns with groove width of 500 nm and 750 nm; 5 μm-wide groove was the most effective in orienting cell directions. They explained that two types of adhered cells co-existed: the cells adhered onto multiple grooves and the cells confined into single groove [31]. Cipriano et al. found that the cells tended to spread over multiple grooves when the groove width was smaller than 5 μm [31]. It was also revealed that the cells spread over multiple grooves were more parallel aligned along the groove when the groove width was smaller than 5 μm. This mechanism may also

help explain endothelial cell responses to the grooved patterns on Ti reported by another study [38]. Both studies showed increased cell proliferation as the groove width decreased from micron level down to nanometer level.

In general, how nanotopography influences cell behaviors have not yet been fully established on cardiovascular-relevant biomaterials. Further comparison and mechanism study on various biomaterials at cellular and biomolecular levels are necessary. It is also important to take into consideration the role of physicochemical properties, chemical compositions and mechanical properties in host cell and tissue responses. As one fundamental field of cardiovascular biomaterials, nanotopography-cell interactions should be considered and studied both *in vitro* and *in vivo* for different cardiovascular applications. One example of *in vitro* applications could be nanostructured scaffolds for cell and/or tissue growth in bioreactors for cell therapies. For *in vivo* studies or clinical applications, cardiovascular devices such as stents and flow diverters that are implanted in the body could take advantage of nanostructures to achieve desirable cellular responses and tissue healing in patients. The *in vitro* applications of nanostructures can be more predictable and the results of *in vitro* studies more repeatable, while the *in vivo* applications still face tremendous challenges due to the complexity of human body and require extensive research in the future.

3. Nanoparticles for cardiovascular applications

Nanoparticles showed promises in a variety of cardiovascular applications due to their unique properties. Unlike bulk implants, nanoparticles are mobile in both intra- and extra-vascular systems, which makes them suitable for selectively delivering drugs and/or serving as imaging agents. Like other nanomaterials, nanoparticles have special properties drastically distinct from their conventional counterparts. Nanoparticles have high surface energy due to their high surface area to volume ratio [5,6]. For this reason, nanoparticles are in a high-energy state, tending to agglomerate together to reduce the energy [5,6]. Thus, necessary measures must be taken to stabilize nanoparticles, and such measures include the use of surfactant, stabilizer, capping reagents, or adjusting the solvent conditions, *e.g.* pH and hydrophilicity/lipophilicity of the dispensing media [72].

Nanoparticles are often used as platforms to be functionalized with other molecules. Multiple functions can be integrated to one nanoparticle. For example, nanoparticles could be conjugated with targeting ligands, such as peptide, to target morbid sites. Nanoparticles could also be conjugated with functional ligands to avoid rapid clearance and phagocytosis. For targeted drug delivery, the conjugated group of nanoparticles should be released in a controllable fashion, which requires special strategies for designing and engineering nanoparticles. Additionally, nanoparticles can be used to enhance biomedical imaging. For example, magnetic nanoparticles (MNPs) as contrast agents could improve magnetic resonance imaging (MRI).

For any nanoparticles designed for clinical applications, their interactions with cells and/or uptake by cells must be specifically considered and carefully studied. Once nanoparticles are able to enter human cells, new applications such as RNA detection and intracellular DNA delivery become possible. Different nanoparticles could have different mechanisms of entering different types of cells; in general, cells could internalize nanoparticles by the process of endocytosis, phagocytosis and pinocytosis, which has been thoroughly reviewed elsewhere [73,74]. Endocytosis and phagocytosis are the specific pathways dependent on protein and receptors, while pinocytosis is a non-specific pathway that happens when cells absorb nearby liquid [73,74]. The presence of both specific and non-specific internalization pathways indicates that most nanoparticles could enter the cells [73,74]. Fig. 2a [75] and 2b [76] are the two examples of internalized nanoparticles located inside cells. The efficacy of cellular uptake of nanoparticles depends on many factors, including surface charge, density, decoration, size, shape, morphology, agglomeration of nanoparticles, and so on. For example, Chithrani [77] investigated how size and shape of gold nanoparticles affected cellular uptake by HeLa cells, as shown in Fig. 3 [77]. The size and aspect ratio were found to greatly influence the uptake of gold nanoparticles into HeLa cells, with maximum uptakes were reached at the size of 50 nm and aspect ratio of 1:1 [77].

3.1. Fabrication approaches for nanoparticles

Fabrication of nanoparticles includes two important steps: synthesis of nanoparticles with desired size and shape, and functionalization of nanoparticles with appropriate surface decorations. Selection of fabrication methods in each step is largely dependent on the material design of nanoparticles and their intended applications. Table 2 summarizes synthesis, decoration, surfactant, capping reagent and functional ligands for some representative nanoparticles.

3.1.1. Synthesis of nanoparticles

Noble metal nanoparticles, *e.g.* gold (Au), silver (Ag), palladium (Pd) and platinum (Pt) nanoparticles, are mostly synthesized via chemical reduction, *e.g.* reducing Au^{3+} to Au atom in $HAuCl_4$ [72], reducing Ag^{+} to Ag atom in $AgNO_3$ [78], reducing Pd^{2+} to Pd atom in K_2PdCl_4 [79], reducing Pt^{4+} to Pt atom in H_2PtCl_6 [79]. Moreover, Ag nanoparticles could reduce Au^{3+} to obtain Au nanoparticles with controllable shape and size following Reaction 1 [78,80]. Ag nanoparticles are more active than Au, Pd and Pt. Thus, Ag nanoparticles could serve as a template to obtain shape-controllable and size-controllable Au, Pd and Pt nanoparticles following the reduction reaction similar to Reaction 1 [78,80]. In recent years, many studies [81–83] also reported the use of natural materials, *e.g.* fungus and plant extracts, to reduce Au^{3+} or Ag^{+} for synthesizing nanoparticles, which showed the potential for scaling up the production of nanoparticles in a green chemistry way.

$$3Ag\ (s) + HAuCl_4\ (aq) \rightarrow Au\ (s) + 3AgCl\ (aq) + HCl\ (aq) \quad (1)$$

Metal oxide nanoparticles are another category of nanoparticles developed for biomedical applications. Wet chemistry precipitation and hydrothermal methods are often used for synthesizing metal oxide nanoparticles. For example, Zheng et al. [84] synthesized Fe_3O_4 magnetic nanoparticles via hydrothermal method. Specifically, $Fe(NO_3)_3 \cdot 9H_2O$ reacted with the reductant, N_2H_4, in water at 160 °C, and in the presence of a surfactant, sodium bis(2-ethylhexyl)sulfosuccinate in a sealed pressure vessel. The produced Fe_3O_4 nanoparticles had a diameter of around 27 nm [84]. In another study, Zhou et al. [85] synthesized Fe_3O_4 nanoparticles using emulsion method in an oil-in-water two-phase solution. Specifically, Fe^{2+} and Fe^{3+} salts were dissolved in the aqueous phase and mixed with cyclohexane which was the oil phase [85]. The pH of this oil-in-water emulsions was then increased to 13.5, resulting in the precipitation of Fe_3O_4 nanoparticles with an average size smaller than 10 nm, as well as a better uniformity than the control Fe3O4 nanoparticles prepared from conventional aqueous precipitation [85]. In addition to Fe_3O_4 nanoparticles, MgO nanoparticles, which is promising for biomedical applications due to its anti-bacterial property [86], were synthesized using sol-gel method [87] or precipitation method [88].

Wet chemistry method has also been widely used for the

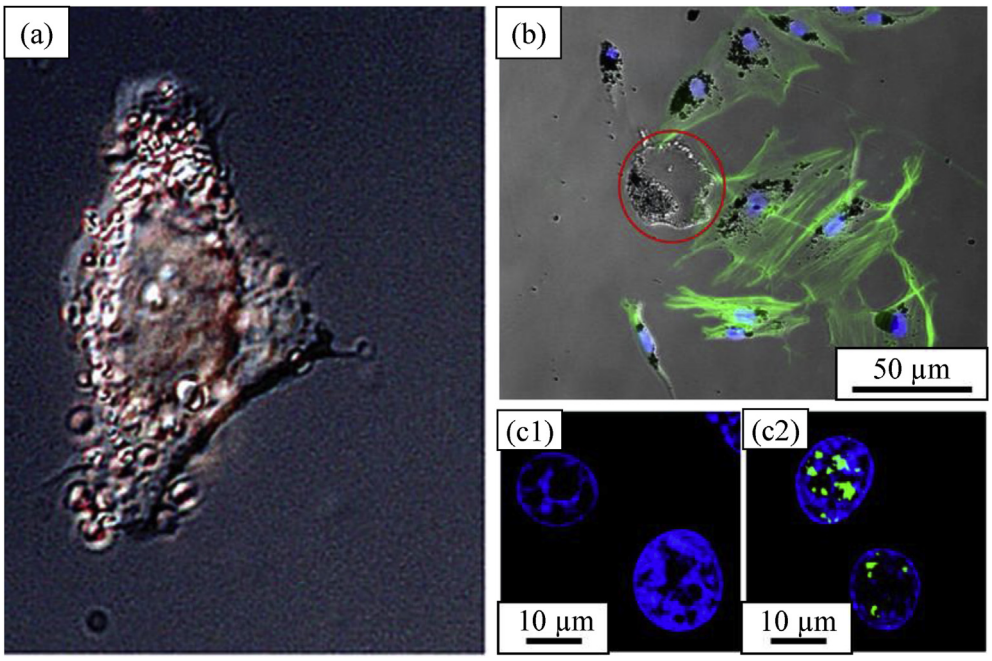

Fig. 2. Examples of internalized nanoparticles. (a) Gold nanoparticles functionalized with peptides were internalized by HepG2 cells after 2 h incubation. Images were taken using a digital color CCD camera. The peptide contained both receptor-mediated endocytosis and nuclear localization signal (Adapted and reprinted with permission from Ref. [75] (Tkachenko AG, Xie H, Coleman D, Glomm W, Ryan J, Anderson MF et al., *Multifunctional gold nanoparticle-peptide complexes for nuclear targeting.* Journal of the American Chemical Society, 2003. **125**(16): p. 4700–4701.). Copyright (2017) American Chemical Society.). (b) Endocytosis of magnetic Fe_3O_4 nanoparticles by bone marrow derived mesenchymal stem cells (BMSCs) after 24-hr incubation. Images were taken using a fluorescence microscope. F-actin of BMSCs were stained as indicated in green color, and nucleus were stained as indicated in blue color. Black dots were the Fe_3O_4 nanoparticles under phase-contrast imaging, and the red circle highlighted the nanoparticles outside of BSMCs. (Adapted and reprinted with permission from Ref. [76] (Zhang N, Lock J, Sallee A, Liu H, *Magnetic nanocomposite hydrogel for potential cartilage tissue engineering: synthesis, characterization, and cytocompatibility with bone marrow derived mesenchymal stem cells.* ACS Applied Materials & Interfaces, 2015. **7**(37): p. 20987–20998.). Copyright (2017) American Chemical Society.). The nucleus of cancer cells (c1) without gold nanoparticles and (c2) in the presence of 0.4 nM nuclear-targeting gold nanoparticles. Nucleus were stained as indicated in blue color, double-strand breaks were stained as indicated in green color. Gold nanoparticles were not stained and not shown. (Adapted and reprinted with permission from Ref. [122] (Kang B, Mackey MA, El-Sayed MA, *Nuclear targeting of gold nanoparticles in cancer cells induces DNA damage, causing cytokinesis arrest and apoptosis.* Journal of the American Chemical Society, 2010. **132**(5): p. 1517–1519.). Copyright (2017) American Chemical Society.). Scale bar = 50 μm for (b), 10 μm for (c1) and (c2).

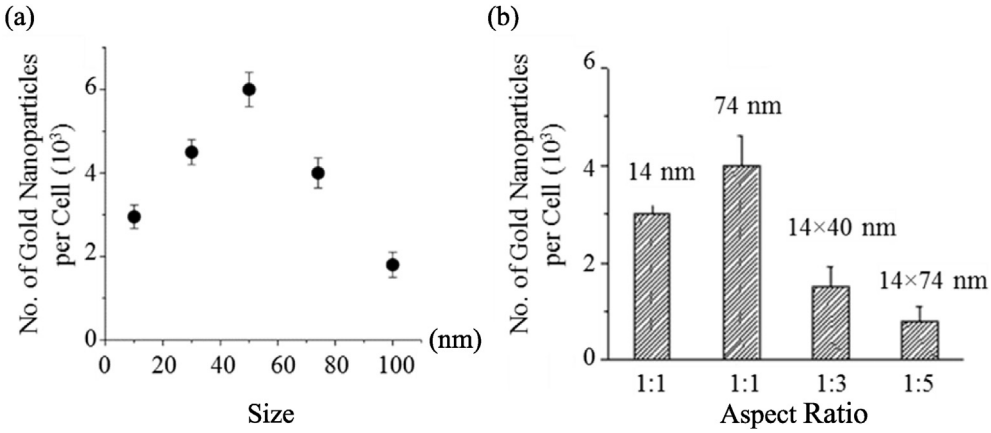

Fig. 3. Cellular uptake of gold nanoparticles was dependent on (a) particle size and (b) aspect ratio. (a) The number of uptaken gold nanoparticles at different sizes. (b) The number of uptaken gold nanoparticles at different aspect ratios. The numbers on top of the bars in (b) shows the length of the two axes which determined the aspect ratio. Aspect ratio 1:1 represents the spherical nanoparticles, and their axis lengths represent the diameter. Adapted and reprinted with permission from Ref. [77] (Chithrani BD, Ghazani AA, Chan WC, *Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells.* Nano letters, 2006. **6**(4): p. 662–668.). Copyright (2017) American Chemical Society.

synthesis of hydroxyapatite (HA) nanoparticles. For example, Liu et al. [89] used the sol-gel method to prepare HA nanoparticles. Wang et al. [90] synthesized HA nanoparticles using hydrothermal precipitation method. Cao et al. [91] and Sun et al. [92] synthesized HA nanoparticles using precipitation methods. A recent study [93] synthesized hierarchical nanostructures on HA microspheres, which could promote protein absorption, promising for drug delivery applications.

3.1.2. *Functionalization of nanoparticles*

The ability to be conjugated with multiple functional groups has greatly extended the potential of nanoparticles in biomedicine. The

Table 2
Summary of fabrication approaches for example nanoparticles.

Nanoparticles	Synthesis Approches	Examplary Surfactant/Capping Reagents	Functionalized Ligands	Examplary Applications	Ref
Au	Chemical reduction, Ag-template Reduction.	Ethylene glycol/PVP, heparin and hyaluronan, citrate	Therapeutic molecules, Peptides, Genes.	Improve conductivity in cardiac patch	[72,78,80–83,94–100,136–142]
Ag	Chemical Reduction	Ethylene glycol/PVP, heparin and hyaluronan, citrate	Therapeutic molecules, Peptides, Genes.	Improve antibacterial property in heart valves	
Pd, Pt	Chemical reduction, Ag-template Reduction.	Sodium citrate, Citric acid/	Proteins	Drug delivery treating cancer	
Fe_3O_4	Wet Chemistry	Sodium bis(2-ethylhexyl)sulfosuccinate/PVA	Dextran, Peptide	Image contrasting agent	[84,85,104,105,143] [144]
PLGA	Wet Chemistry	Covalently Immobilized PLGA on ePTFE grafts by H_2O_2/H_2SO_4 and aminolyzation	Drug Molecules. Isothiocynate-Dextran	Increased presence of pre-loaded drug over vascular graft	[102]
Polyester Carbon Nanotubes	Wet Chemistry	Functionalized with nitric and sulfuric acid	Dispersion in pre-polymer solution for scaffold fabrication	Improved electrical conductivity and strength in scaffolds for tissue regeneration	[103,145]
PEGylated Liposome	Wet Chemistry and Membrane Extrusion	Activation with NHS	Cytokines. Growth factors.	A vehicle for site specific targeting and delivery within the heart, post MI	[146]
Amino Acid Target		Linked covalently to a scrambled peptide targeter	Drug Molecules.		
Lecithin VEGF Pluronic F-127 Core/Shell	Wet Chemistry Sonication	The core/shell nanoparticles were introduced to Capryol 90 to induce gelation at physiological temperature	Pluronic F-127	Site specific regeneration of cardiac tissue post MI	[147]
Lipidoid	Wet Chemistry Self Assembly	Nanoprecipitation for both Lipidoid and ModRNA	Modified mRNA	Increase the potential of gene therapy to improve cardiovascular regeneration	[148]

methodologies for functionalizing nanoparticles and related applications have been thoroughly reviewed elsewhere [94–96]. Gold nanoparticles, for example, have attracted broad interests for functionalization due to its chemical stability. The conjugated groups are supposed to complete certain missions due to their unique properties. Such missions include, but not limited to targeting cells [97,98], improving the cellular uptake of the nanoparticles, carrying and releasing therapeutic agents or genes [99]. The functional groups can be conjugated via physical absorption [94–96,100] or chemical bonding [94–96,100]. The chemical bonding attracted more interests due to stronger adhesion and stability. The “chemical-bond bridge” between nanoparticles and functional groups could be produced by either replacing the existent ligand, *e.g.* the surfactant, with new ligand, or adding the new ligand [94–96,100]. An example of successful gold nanoparticle functionalization is reported in the work of Polizzi et al. who fabricated monolayer-protected gold clusters (MPCs) capable of releasing nitric oxide (NO) [99], which facilitates many physiological processes and supports the healthy function of the cardiovascular system [101]. A scalable fashion of controlled release of NO between 0.007 and 0.386 micromole per milligram was achieved by chemically binding gold nanoparticles with polyamine [99]. Thus, functionalization of nanoparticles is effective in enhancing the performance of nanoparticles and expanding their applications.

3.1.3. Polymeric nanoparticles

Cardiovascular engineering and regenerative medicine employ a range of different nanoparticle types, fabrication methods, and uses for future medical applications. While there are many types of nanoparticles in use, polymeric nanoparticles are of key interest based on their tunable properties, and potential for reabsorption within the body. They can be free floating, or coupled with another material, for example, as reported in the work of Meslmani et al. [102]. The focus of their research was to immobilize poly(lactic-*co*-glycolic) acid (PLGA) on polytetrafluoroethylene (ePTFE) films as a promising material for developing vascular grafts [102]. The researchers used this approach to develop a potential vehicle for delivery of specific molecules; such as antithrombotic drugs to act in opposition to the regular side effects of thrombosis [102]. Another method for incorporating polymers with nanomaterials for cardiovascular applications is seen in the work completed by Ahadian et al. The focus of the research was to develop a scaffold composed of polyester and carbon nanotubes [103]. One of the favorable characteristics associated with this approach is the increase in stability and electrical conductivity when carbon nanotubes are included in the composite material, which enables future applications in cell-cell coupling [103]. Clearly, there is still much to room to develop additional polymeric nanoparticles for cardiovascular applications and with the positive effects observed in composite materials [103]. Future research is needed to promote successful applications of polymeric nanoparticles in cardiovascular treatments.

3.2. Nanoparticles for the diagnosis of cardiovascular diseases

Nanoparticles can be used in many diagnostic applications of CVDs because it can be engineered to target specific morbid sites while being detected. An example is the use of nanoparticles in the early diagnosis of atherosclerosis. Atherosclerosis often leads to myocardial infarction and stroke, but it could be identified in early stage by detecting inflammatory level. The success of an early diagnosis massively depends on the noninvasive diagnosis in the early stage. To achieve this goal, Nahrendorf et al. [104] fabricated monocrystalline magnetic nanoparticles (MNPs) for detecting vascular cell adhesion molecule-1 (VCAM-1), an indicator of inflammation. The multivalent MNPs in this study were decorated with peptide that could target the MNPs to the cells that were expressing VCAM-1 [104]. The MNPs can determine whether the inflammation is occurring and what was the degree of it, providing an opportunity to identify atherosclerosis in its early stage [104].

In the domain of MRI diagnosis, the merits of nanoparticles have been exploited as well. Nanoparticles could be ideal contrast agents for MRI which have targeting function. The general idea is to transport nanoparticles to the target site and have the density and position of nanoparticles detected in MRI. MRI technology combined with nanoparticles is less invasive than traditional biopsy method. A successful example is the imaging of rejection site after transplantation of rat cardiac allograft [105]. Kanno et al. [105] fabricated a novel dextran-coated ultrasmall superparamagnetic iron oxide particles. The macrophages were successfully labeled by the MNPs, and the signal generated by MNPs indicated the location and degree of rejection [105]. Considering macrophages can be successfully detected, the foreign body responses and inflammatory responses may also be evaluated in many other cardiovascular-relevant conditions in the future using similar approaches. It is safe to say the nanoparticles hold tremendous potentials to enable new diagnostic methods for cardiac and cardiovascular applications.

3.3. Nanoparticles for targeted drug delivery

Nanoparticle platform has big potential to realize targeted drug delivery for their superior multi-functionality. Carrying and releasing drug, and targeting the morbid site are the most essential functions for a successful targeted drug-delivery nanoparticle. For example, Polizzi et al. [99] fabricated functionalized gold nanoparticles for controlled release of nitric monoxide (NO). They achieved the tunable releasing profile by choosing different ligand [99]. NO can mediate endothelium and vascular smooth muscle cells functions [101,106–108]. It was shown that NO-releasing polymers inhibit DNA synthesis of smooth muscle cells [109].

Nanoparticles combining imaging and therapeutic functions are often termed as theranostic nanoparticles, which could help to realize the concept of personalized medicine. They are usually designed as a platform with functional groups integrated. For example, McCarthy et al. [110] conjugated a photosensitizer to a dextran-coated magnetofluorescent nanoparticle targeting plaque macrophages. The photosensitizer could release oxygen singlet upon light of certain wavelength range, and the released oxygen could kill macrophages [110]. This detecting and killing of macrophages were quite significant for the future diagnosis and therapy of atherosclerosis [110]. It can be predicted that the integration of imaging and therapeutic functions in one nanoparticle platform could empower many successful applications in targeted drug delivery.

Apart from conjugating therapeutically functional groups to the drug-loading nanoparticles, the drug can also be encapsulated by nanoparticles. Liposomes are an ideal candidate for encapsulating drugs. Danenberg et al. [111] studied a liposomes nanoparticles with clodronate encapsulated inside. This *in vivo* studies in rat and rabbit models demonstrated that this drug release system significantly reduced neointimal hyperplasia after balloon injury.

Instead of being a platform for functional groups, some nanoparticles themselves possess therapeutic efficacy. For example, silver nanoparticles were reported to be anti-platelet, depending on particle size [112]; MgO nanoparticles were found to have antibacterial properties [86], which could reduce infections associated with medical implants and devices. These nanoparticles can be used as therapeutic agents and delivered by matrix materials.

3.4. Toxicity of nanoparticles and nanomaterials

Nanoparticles possess attractive properties for increasing efficacy of cardiovascular treatments; however, it is vital to fully understand cytotoxic effects associated with their use. The toxicity of nanoparticles should be particularly considered due to its mobility in circulation throughout the human body, an essential difference from the other two categories of nanomaterials reviewed in this paper, i.e., nanostructured surfaces and nanocomposites. The toxicity of nanocomposites could largely ascribe the toxicity to their nanoparticle components when a well-known biocompatible material is used as the matrix, for example the polymers that have been used in FDA approved products. While the use of nanoparticles in cardiovascular applications remains a growing field, recent studies have indicated specific cytotoxic effects associated with cardiovascular system upon exposure to different varieties of nanoparticles [91,113–117]. For example, studies have shown that ultra-small superparamagnetic iron oxide nanoparticles (USPIO), composed of magnetite Fe_3O_4 with <1.0% stabilizing ligands of poly ethylene glycol, have adverse effects on myocardium, e.g., thrombotic response *in vivo*, platelet aggregation *in vitro* with whole blood, DNA damage and increase of cardiac oxidative stress [118]. Such effects were discovered after a study intravenously introduced 4–5 nm diameter USPIOs at 0.4, 2, 10 micrograms/kg into mice; consequently, researchers assessed thrombotic response after the exposure time of one hour [118]. In addition to iron oxide nanoparticles, nano-sized zerovalent iron particles were also found to produce toxic results related to pulmonary and cardiovascular systems [119]. When nano-sized zerovalent iron particles were in the presence of a co-culture of human EA.hy926 vascular endothelial cells and human A549 alveolar epithelial cells, researchers found an increased level of oxidative stress in both cell types [119]. The researchers also found that inflammatory factors were increased within the alveolar epithelial cells [119]. Although Fe-based nanoparticles showed great potential for biomedical applications, their impact to human health and environment during their lifetime should be studied carefully and taken into special consideration before wide-spread use.

Carbon-based nanomaterials were also often associated with their safety concern, although carbon nanoparticles (CNP) and nanotubes (CNT) have received praise for their positive results in a myriad of medical and environmental applications. For instance, researchers found that the culture of aortic endothelial cells in proximity with either single wall CNT (SWCNT) or double wall CNT (DWCNT), decreased cellular viability [114]. And the administration of SWCNTs or DWCNTs, via pharyngeal aspiration in mice, elevated monocyte adhesion directly to endothelial cells, thus leading to atherosclerogenesis [114]. Formation of atherosclerotic plaques represents a dangerous path towards future cardiovascular diseases and dysfunction. In another study, researchers determined that the levels of acute phase response proteins (ARP) were significantly elevated by MWCNT [120], and an increased ARP levels in plasma are considered an indication of danger of cardiovascular disease [121]. Aside from Fe-based and C-based nanoparticles, gold nanoparticles, which were widely regarded as “bio-inert” and “biocompatible”, were also found to possibly damage DNA as shown in Fig. 2c1 and 2c2 [122]. In Fig. 2c2, the DNA double-strands damage was stained and shown with green color in the presence of 0.4 M gold nanoparticles, while no damage was shown in the absence of the gold nanoparticles [122].

Clearly, toxicity considerations are of the utmost importance when selecting any nanomaterial for applications in regenerative medicine and tissue engineering. From tissue level to cellular level, and even the intracellular environment and cell nucleus, the toxicity of nanoparticles remains a major concern to the use of nanoparticles. Even though the nanomaterial in question may have exceptional properties, such materials must first pass the test of toxicity before being used in any biomedical application. While many of the research findings and cardiotoxic effects detailed in this section may be the causes for concern, it is essential to remember that incorporating nanomaterials into cardiovascular

regenerative treatments is still a relatively new field. To fully understand its toxicity, researchers should also look into many other topics about foreign body responses and immunological responses, particularly specified in hemotoxicity and inflammatory responses. These properties were thoroughly reviewed elsewhere [123–128]. Further researches will be needed to mitigate and address the concerns associated with toxicity.

4. Nanocomposites for cardiovascular applications

Single phase materials may not meet the stringent requirements for cardiovascular applications. Heart valve and cardiac patch are the two examples that require both good mechanical properties and biological performances. For example, heart valves need to tolerate repeating cycles of mechanical load for years and even lifelong, while at the same time, interact with biological environment. Foreign body responses, immunological responses and shearing force of flowing blood make the material interactions with cardiovascular systems complicated and raise a set of stringent criteria for the properties of materials. Nanocomposites may provide a chance to overcome the limit of conventional single-phase materials. A representative solution is to use nanomaterials as the second phase to reinforce matrix polymers. The second phase nanomaterials are supposed to tailor mechanical properties of matrix polymers, and may also tune the host responses to the materials. Fabrication of representative nanocomposite systems and their applications will be discussed in this section.

4.1. Fabrication approaches of nanocomposites

A typical nanocomposite material consists of a matrix material that could be metal, polymer, ceramic or a combination of any of them, and a functional component that is at nanometer size in at least one dimension. Fabrication approaches for nanocomposites mostly involve these key steps, e.g., preparing the matrix and nanoscale component, and dispersing the nanomaterial component into the matrix. Preparation for the nanoscale component is mostly similar to the fabrication approaches as described above in the synthesis of nanoparticles (see Table 2). After obtaining nanoscale component, the following step typically is to disperse the nanoscale components into the matrix. During dispersion, the formation of aggregates should be carefully avoided to maintain the nanoscale size of the dispersed phases in order to harvest the special properties of nano-features. Using surfactant could be an effective way to keep nanoparticles from aggregating, but surfactants may raise additional concerns on toxicity and requires additional studies on biocompatibility for biomedical applications [129]. Mechanical dispersion is a straightforward method that is widely used, since it breaks agglomerates by merely mechanical forces. A widely-used mechanical method is to use high-power ultrasonic energy to disperse ceramic particles, *e.g.* nano-hydroxyapatite [130] or nano-TiO_2 [129], into polymer matrix. The ultrasound provides adequately high energy to overcome certain aggregation of nanoparticles that does not involve strong chemical bonding, e.g., aggregation caused by physical interactions. Alternatively, electrochemical method is a well-controlled process to produce nanocomposites on a conductive substrate. For example, a polymer-based nanocomposite coatings reinforced by nano-hydroxyapatite were successfully prepared on Mg substrates using electrophoretic deposition [131,132].

4.2. Nanocomposites for artificial heart valve

Heart valves allow unidirectional flow of blood in and out heart chambers. Malfunction of heart valve leads to severe health threat and even death. In such case, heart valve replacement surgery is needed. In addition to decellularized tissue, synthetic materials such as polymers, are often used to fabricate artificial heart valves. Due to the high requirements of mechanical properties and antiplatelet performance, nanocomposites become promising candidate materials. Integrating the reinforcing phase to polymer matrix could push the limit of performance of the sole polymer matrix, achieving both desired mechanical properties and biological performances.

Much progress has been made to engineer nanocomposites for artificial heart valves. For example, Kidane et al. [23] fabricated a polyurethane nanocomposite reinforced by polycarbonate soft segment and polyhedral-oligomeric-silsesquioxanes (POSS-PCU) nanoparticles. The POSS-PCU demonstrated impressive mechanical properties and antiplatelet properties as heart valve leaflets. Their results showed that POSS nanoparticles increased the tensile strength, the elongation at break, the Young's modulus and the tear strength of PCU at 37 °C.

Despite that continuing enhancements of polymer-based materials have been made for artificial heart valves, mechanical failure still cannot be completely avoided because synthetic materials are essentially a target of foreign body responses [133]. Stiffening and tearing of artificial heart valves resulted from calcification are the major concerns [133]. Nanocomposites could significantly improve multiple properties as compared with a single phase material and provide an opportunity to address these problems; however, further research is still necessary to increase the efficacy of nanocomposites.

4.3. Nanocomposites for cardiac patch

Developing a bioactive and mechanically supportive construct to repair damaged cardiac tissue is absolutely vital. Cardiac patch is a scaffold designed to support and regenerate myocardium post-myocardial infarction, or other ischemic insult to the tissue. A cardiac patch should induce local cardiac tissue regeneration, so that the damaged heart can return to proper functions. Several aspects should be considered when designing a cardiac patch, including mechanical properties, hemocompatibility, antiplatelet property and the capacity of facilitating tissue regeneration. Cardiac patch can either be bioresorbable (temporary) or non-resorbable (permanent); the permanent patch will require secondary surgery to remove while the temporary patch could be resorbed naturally over time.

Various nanocomposites demonstrated their potentials for this application. For example, a carbon nanofiber-reinforced PLGA nanocomposite successfully promoted adhesion and proliferation of cardiomyocytes and neurons, and thus was promising to fabricate conductive cardiac patch with desirable host responses [24]. Also, Shevach et al. [25] fabricated a gold nanoparticles-reinforced polymer fibers scaffolds for the cardiac patch. Their gold nanoparticles were evaporated and deposited onto electrospun fibers composed of polycaprolactone and gelatin [25]. The nanoparticle/fiber 3D composites significantly increased the amplitude and rates of contraction of cardiac tissues that were seeded and grown on them, suggesting their potential in the regenerative treatment of heart infarction [25]. Beyond serving as a structural supporting device, cardiac patches made of nanocomposites also have the potentials for cell delivery applications as studied by Chen et al. [26]. In their study, a Bioglass®-reinforced poly(glycerol sebacate) (PGS) composite was fabricated and the Bioglass® nanoparticles neutralized acidic degradation products of PGS, which increased the biocompatibility of the PGS matrix [26]. The reinforced nanocomposite was more suitable for cell delivery than plain PGS, attributing to the increased biocompatibility [26].

Generally, adding biologically active components could enhance the overall performance of cardiac patches. Researchers have indicated that incorporation of proteins within a synthetic polymer can induce favorable biological responses to the patches [115–117]. For example, one group of researchers incorporated zien, a corn protein, into an electrospun PGS cardiovascular patch and improved the stiffness and water uptake of the patch [115]. Not just the mechanical and hygroscopic property can be enhanced, biological responses can also be tuned to a favorable direction by the nanocomposites consisting of biological components. Another study showed that the addition of silk to a decellularized cardiac tissue matrix can improve vascularization [116].

Overall, nanocomposites constitute a promising approach to strengthening cardiovascular patch designs. Current progress of cardiac patch seemed promising, but the questions of "How do we increase the mechanical properties of the patch, while maintaining its overall bioactivity?" and "How do we scale up the patch from benchtop to bedside?" still lie ahead. However, nanocomposites may hold the key to future success and deserve extensive research and development in the future.

5. Conclusions

The treatments of cardiovascular diseases have been revolutionized by biomaterials-based technologies, including various devices and implants. Nanomaterials have already gained great success in many fields such as electronics and aeronautics. When nanomaterials are introduced to face biomedical challenges, essential breakthroughs could be expected because the efficacy of conventional materials can be significantly enhanced when they are transformed into nanomaterials. New strategies for different applications will emerge with the advancement of nanoscience and nanotechnologies. Predictably, the treatments of CVDs will be further improved and even transformed as more promises in nanomaterials are becoming reality. This review introduced the nanostructured surfaces, nanoparticles and nanocomposites for CVD treatments. We examined theoretical foundations necessary for understanding the field of nanomaterials in cardiovascular applications, and introduced important examples of cardiovascular nanomaterials that are inspiring to future work toward clinical translation. While clinical translation still remains in its infancy, nanomaterials will predictably yield a variety of treatments patients with CVDs. The future success of nanomaterials for treating CVDs could be largely dependent on exploring new solutions for current clinical challenges using nanomaterials, and establishing a more thorough understanding of interactions between material and human body. In addition to mechanical properties and toxicity, more characteristics of nanomaterials should be thoroughly considered for cardiovascular applications, such as anti-microbial properties, foreign body reactions and tissue-regenerating functions. The consideration of a successful biomaterial has also been extended from the sole bio-inertness to bioactivity, biodegradability and anti-infection. Nanomaterials are promising in the foreseeable future to address clinical challenges.

References

[1] World Health Organization, Factsheets, Cardiovascular Diseases (CVDs), 2017. http://www.who.int/mediacentre/factsheets/fs317/en/.

[2] M. Dariush Mozaffarian, Emelia J. Benjamin, Alan S. Go, Donna K. Arnett, Michael J. Blaha, Mary Cushman, Sarah de Ferranti, Jean-Pierre Després, Heather J. Fullerton, Virginia J. Howard, Mark D. Huffman, Suzanne E. Judd, Brett M. Kissela, Daniel T. Lackland, Judith H. Lichtman, Lynda D. Lisabeth, Simin Liu, Rachel H. Mackey, David B. Matchar, Darren K. McGuire, Emile R. Mohler III, Claudia S. Moy, Paul Muntner, Michael E. Mussolino, Khurram Nasir, Robert W. Neumar, Graham Nichol, Latha Palaniappan, Dilip K. Pandey, Mathew J. Reeves, Carlos J. Rodriguez, Paul D. Sorlie, Joel Stein, Amytis Towfighi, Tanya N. Turan, Salim S. Virani, Joshua Z. Willey, Daniel Woo, Robert W. Yeh, Melanie B. Turner, on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Heart disease and stroke Statistics—2015 update (a report from the American heart association), Circulation 131 (2015) e29–e322.

[3] D.L. Hoyert, J. Xu, Deaths: preliminary data for 2011, Natl. Vital Stat. Rep. 61 (6) (2012) 1–51.

[4] M.J. Hall, C.J. DeFrances, S.N. Williams, A. Golosinskiy, A. Schwartzman, National hospital discharge survey: 2007 summary, Natl. Health Stat. Rep. 29 (29) (2010) 1–20.

[5] H. Liu, T.J. Webster, Nanomedicine for implants: a review of studies and necessary experimental tools, Biomaterials 28 (2) (2007) 354–369.

[6] W. Jiang, H. Liu, Nanocomposites for bone repair and osteointegration with soft tissues, Nanocomposites Musculoskelet. Tissue Regen. (2016) 241.

[7] J.-Y. Rho, L. Kuhn-Spearing, P. Zioupos, Mechanical properties and the hierarchical structure of bone, Med. Eng. Phys. 20 (2) (1998) 92–102.

[8] S. Weiner, W. Traub, Bone structure: from angstroms to microns, FASEB J. 6 (3) (1992) 879–885.

[9] T.J. Webster, C. Ergun, R.H. Doremus, R.W. Siegel, R. Bizios, Enhanced osteoclast-like cell functions on nanophase ceramics, Biomaterials 22 (11) (2001) 1327–1333.

[10] T.G. Kim, S.-H. Park, H.J. Chung, D.-Y. Yang, T.G. Park, Microstructured scaffold coated with hydroxyapatite/collagen nanocomposite multilayer for enhanced osteogenic induction of human mesenchymal stem cells, J. Mater. Chem. 20 (40) (2010) 8927–8933.

[11] T.J. Webster, C. Ergun, R.H. Doremus, R.W. Siegel, R. Bizios, Enhanced functions of osteoblasts on nanophase ceramics, Biomaterials 21 (17) (2000) 1803–1810.

[12] A.F. Cipriano, J. Lin, C. Miller, A. Lin, M.C.C. Alcaraz, P. Soria Jr., H. Liu, Anodization of magnesium for biomedical applications–Processing, characterization, degradation and cytocompatibility, Acta Biomater. 62 (2017) 397–417.

[13] I. Johnson, W. Jiang, H. Liu, The effects of serum proteins on magnesium alloy degradation in vitro, Sci. Rep. 7 (1) (2017) 14335.

[14] J. Park, S. Bauer, K. von der Mark, P. Schmuki, Nanosize and vitality: TiO2 nanotube diameter directs cell fate, Nano Lett. 7 (6) (2007) 1686–1691.

[15] S. Oh, K.S. Brammer, Y.J. Li, D. Teng, A.J. Engler, S. Chien, S. Jin, Stem cell fate dictated solely by altered nanotube dimension, Proc. Natl. Acad. Sci. 106 (7) (2009) 2130–2135.

[16] K.S. Brammer, S. Oh, J.O. Gallagher, S. Jin, Enhanced cellular mobility guided by TiO2 nanotube surfaces, Nano Lett. 8 (3) (2008) 786–793.

[17] H.-A. Pan, Y.-C. Hung, Y.-P. Sui, G.S. Huang, Topographic control of the growth and function of cardiomyoblast H9c2 cells using nanodot arrays, Biomaterials 33 (1) (2012) 20–28.

[18] J. Lu, T.J. Webster, Reduced immune cell responses on nano and submicron rough titanium, Acta Biomater. 16 (2015) 223–231.

[19] J. Lu, D. Khang, T.J. Webster, Greater endothelial cell responses on submicron and nanometer rough titanium surfaces, J. Biomed. Mater. Res. Part A 94 (4) (2010) 1042–1049.

[20] J. Lu, C. Yao, L. Yang, T.J. Webster, Decreased platelet adhesion and enhanced endothelial cell functions on nano and submicron-rough titanium stents, Tissue Eng. Part A 18 (13–14) (2012) 1389–1398.

[21] A.W. Carpenter, M.H. Schoenfisch, Nitric oxide release: Part II. Therapeutic applications, Chem. Soc. Rev. 41 (10) (2012) 3742–3752.

[22] P.W. Serruys, M.J. Kutryk, A.T. Ong, Coronary-artery stents, N. Engl. J. Med. 354 (5) (2006) 483–495.

[23] A.G. Kidane, G. Burriesci, M. Edirisinghe, H. Ghanbari, P. Bonhoeffer, A.M. Seifalian, A novel nanocomposite polymer for development of synthetic heart valve leaflets, Acta Biomater. 5 (7) (2009) 2409–2417.

[24] D.A. Stout, B. Basu, T.J. Webster, Poly (lactic–co-glycolic acid): carbon nanofiber composites for myocardial tissue engineering applications, Acta Biomater. 7 (8) (2011) 3101–3112.

[25] M. Shevach, B.M. Maoz, R. Feiner, A. Shapira, T. Dvir, Nanoengineering gold particle composite fibers for cardiac tissue engineering, J. Mater. Chem. B 1 (39) (2013) 5210–5217.

[26] Q. Chen, L. Jin, W.D. Cook, D. Mohn, E.L. Lagerqvist, D.A. Elliott, J.M. Haynes, N. Boyd, W.J. Stark, C.W. Pouton, Elastomeric nanocomposites as cell delivery vehicles and cardiac support devices, Soft Matter 6 (19) (2010) 4715–4726.

[27] A. del Campo, E. Arzt, Fabrication approaches for generating complex micro- and nanopatterns on polymeric surfaces, Chem. Rev. 108 (3) (2008) 911–945.

[28] Y. Yan, M. Zhang, C.H. Moon, H.-C. Su, N.V. Myung, E.D. Haberer, Viral-templated gold/polypyrrole nanopeapods for an ammonia gas sensor, Nanotechnology 27 (32) (2016), 325502.

[29] C. Li, C. Liu, W. Wang, Z. Mutlu, J. Bell, K. Ahmed, R. Ye, M. Ozkan, C.S. Ozkan, Silicon derived from glass bottles as anode materials for lithium ion full cell batteries, Sci. Rep. 7 (1) (2017) 917.

[30] Y.-Y. Song, F. Schmidt-Stein, S. Bauer, P. Schmuki, Amphiphilic TiO2 nanotube arrays: an actively controllable drug delivery system, J. Am. Chem. Soc. 131 (12) (2009) 4230–4232.

[31] A.F. Cipriano, N. De Howitt, S.C. Gott, C. Miller, M.P. Rao, H. Liu, Bone marrow stromal cell adhesion and morphology on micro-and sub-micropatterned titanium, J. Biomed. Nanotechnol. 10 (4) (2014) 660–668.

[32] T.F. Lüscher, J. Steffel, F.R. Eberli, M. Joner, G. Nakazawa, F.C. Tanner, R. Virmani, Drug-eluting stent and coronary thrombosis biological

mechanisms and clinical implications, Circulation 115 (8) (2007) 1051–1058.
[33] M. Joner, A.V. Finn, A. Farb, E.K. Mont, F.D. Kolodgie, E. Ladich, R. Kutys, K. Skorija, H.K. Gold, R. Virmani, Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk, J. Am. Coll. Cardiol. 48 (1) (2006) 193–202.
[34] C.M. Matter, I. Rozenberg, A. Jaschko, H. Greutert, D.J. Kurz, S. Wnendt, B. Kuttler, H. Joch, J. Grünenfelder, G. Zünd, Effects of tacrolimus or sirolimus on proliferation of vascular smooth muscle and endothelial cells, J. Cardiovasc. Pharmacol. 48 (6) (2006) 286–292.
[35] M. Lampin, R. Warocquier-Clérout, C. Legris, M. Degrange, M. Sigot-Luizard, Correlation between substratum roughness and wettability, cell adhesion, and cell migration, J. Biomed. Mater. Res. 36 (1) (1997) 99–108.
[36] S. Hitchcock, N. Carroll, M. Nicholas, Some effects of substrate roughness on wettability, J. Mater. Sci. 16 (3) (1981) 714–732.
[37] Y. Wang, L. Zhang, L. Sun, T.J. Webster, Increased healthy osteoblast to osteosarcoma density ratios on specific PLGA nanopatterns, Int. J. Nanomed. 8 (2013) 159.
[38] J. Lu, M.P. Rao, N.C. MacDonald, D. Khang, T.J. Webster, Improved endothelial cell adhesion and proliferation on patterned titanium surfaces with rationally designed, micrometer to nanometer features, Acta Biomater. 4 (1) (2008) 192–201.
[39] L. Zhang, T.J. Webster, Nanotechnology and nanomaterials: promises for improved tissue regeneration, Nano Today 4 (1) (2009) 66–80.
[40] H.S. Yang, N. Ieronimakis, J.H. Tsui, H.N. Kim, K.-Y. Suh, M. Reyes, D.-H. Kim, Nanopatterned muscle cell patches for enhanced myogenesis and dystrophin expression in a mouse model of muscular dystrophy, Biomaterials 35 (5) (2014) 1478–1486.
[41] H.N. Kim, D.-H. Kang, M.S. Kim, A. Jiao, D.-H. Kim, K.-Y. Suh, Patterning methods for polymers in cell and tissue engineering, Ann. Biomed. Eng. 40 (6) (2012) 1339–1355.
[42] S.J. Liliensiek, J.A. Wood, J. Yong, R. Auerbach, P.F. Nealey, C.J. Murphy, Modulation of human vascular endothelial cell behaviors by nanotopographic cues, Biomaterials 31 (20) (2010) 5418–5426.
[43] D.C. Miller, A. Thapa, K.M. Haberstroh, T.J. Webster, Endothelial and vascular smooth muscle cell function on poly (lactic-co-glycolic acid) with nanostructured surface features, Biomaterials 25 (1) (2004) 53–61.
[44] A. Thapa, T.J. Webster, K.M. Haberstroh, Polymers with nano-dimensional surface features enhance bladder smooth muscle cell adhesion, J. Biomed. Mater. Res. Part A 67 (4) (2003) 1374–1383.
[45] L. Weng, T.J. Webster, Nanostructured magnesium has fewer detrimental effects on osteoblast function, Int. J. Nanomed. 8 (2013) 1773.
[46] A.F. Cipriano, N. De Howitt, S.C. Gott, C.T. Miller, M.P. Rao, H. Liu, Bone marrow stromal cell adhesion and morphology on micro- and submicropatterned titanium, J. Biomed. Nanotechnol. 10 (4) (2014) 660–668.
[47] F. Luo, L. Heyderman, H. Solak, T. Thomson, M. Best, Nanoscale perpendicular magnetic island arrays fabricated by extreme ultraviolet interference lithography, Appl. Phys. Lett. 92 (10) (2008), 102505.
[48] G. Feiertag, W. Ehrfeld, H. Freimuth, H. Kolle, H. Lehr, M. Schmidt, M. Sigalas, C. Soukoulis, G. Kiriakidis, T. Pedersen, Fabrication of photonic crystals by deep x-ray lithography, Appl. Phys. Lett. 71 (11) (1997) 1441–1443.
[49] C. Cuisin, A. Chelnokov, J.-M. Lourtioz, D. Decanini, Y. Chen, Submicrometer resolution Yablonovite templates fabricated by x-ray lithography, Appl. Phys. Lett. 77 (6) (2000) 770–772.
[50] F. Rousseaux, D. Decanini, F. Carcenac, E. Cambril, M. Ravet, C. Chappert, N. Bardou, B. Bartenlian, P. Veillet, Study of large area high density magnetic dot arrays fabricated using synchrotron radiation based x-ray lithography, J. Vac. Sci. Technol. B 13 (6) (1995) 2787–2791.
[51] R.K. Pal, N.E. Kurland, S.C. Kundu, V.K. Yadavalli, in: Fabrication of Silk Microstructures Using Photolithography, MRS Proceedings, Cambridge Univ Press, 2015, pp. 163–170.
[52] I. Mironi-Harpaz, L. Hazanov, G. Engel, D. Yelin, D. Seliktar, In-situ architectures designed in 3D cell-laden hydrogels using microscopic laser photolithography, Adv. Mater. 27 (11) (2015) 1933–1938.
[53] T. Limongi, R. Schipani, A. Di Vito, A. Giugni, M. Francardi, B. Torre, M. Allione, E. Miele, N. Malara, S. Alrasheed, Photolithography and micromolding techniques for the realization of 3D polycaprolactone scaffolds for tissue engineering applications, Microelectron. Eng. 141 (2015) 135–139.
[54] K.Y. Suh, H.H. Lee, Capillary force lithography: large-area patterning, self-organization, and anisotropic dewetting, Adv. Funct. Mater. 12 (6–7) (2002) 405–413.
[55] K.Y. Suh, Y.S. Kim, H.H. Lee, Capillary force lithography, Adv. Mater. 13 (18) (2001) 1386.
[56] K.Y. Suh, R. Langer, Microstructures of poly (ethylene glycol) by molding and dewetting, Appl. Phys. Lett. 83 (8) (2003) 1668–1670.
[57] K. Hon, L. Li, I. Hutchings, Direct writing technology—advances and developments, CIRP Annal. Manuf. Technol. 57 (2) (2008) 601–620.
[58] S. Jegadesan, S. Sindhu, R.C. Advincula, S. Valiyaveettil, Direct electrochemical nanopatterning of polycarbazole monomer and precursor polymer films: ambient formation of thermally stable conducting nanopatterns, Langmuir 22 (2) (2006) 780–786.
[59] B.W. Maynor, S.F. Filocamo, M.W. Grinstaff, J. Liu, Direct-writing of polymer nanostructures: poly (thiophene) nanowires on semiconducting and insulating surfaces, J. Am. Chem. Soc. 124 (4) (2002) 522–523.
[60] S.-E. Lai, Y.-J. Hong, Y.-T. Chen, Y.-T. Kang, P. Chang, T.-R. Yew, Direct-writing of Cu nano-patterns with an electron beam, Microsc. Microanal. 21 (06) (2015) 1639–1643.
[61] K.S. Toohey, N.R. Sottos, J.A. Lewis, J.S. Moore, S.R. White, Self-healing materials with microvascular networks, Nat. Mater. 6 (8) (2007) 581–585.
[62] D. Therriault, S.R. White, J.A. Lewis, Chaotic mixing in three-dimensional microvascular networks fabricated by direct-write assembly, Nat. Mater. 2 (4) (2003) 265–271.
[63] J.A. Lewis, Direct ink writing of 3D functional materials, Adv. Funct. Mater. 16 (17) (2006) 2193–2204.
[64] T.D. Brown, P.D. Dalton, D.W. Hutmacher, Direct writing by way of melt electrospinning, Adv. Mater. 23 (47) (2011) 5651–5657.
[65] M. Rasekh, Z. Ahmad, R. Day, A. Wickam, M. Edirisinghe, Direct writing of polycaprolactone polymer for potential biomedical engineering applications, Adv. Eng. Mater. 13 (9) (2011) B296–B305.
[66] R. Gaetani, P.A. Doevendans, C.H. Metz, J. Alblas, E. Messina, A. Giacomello, J.P. Sluijter, Cardiac tissue engineering using tissue printing technology and human cardiac progenitor cells, Biomaterials 33 (6) (2012) 1782–1790.
[67] T. Lei, C. Ouyang, W. Tang, L.-F. Li, L.-S. Zhou, Preparation of MgO coatings on magnesium alloys for corrosion protection, Surf. Coatings Technol. 204 (23) (2010) 3798–3803.
[68] A.F. Cipriano, C. Miller, H. Liu, Anodic growth and biomedical applications of TiO2 nanotubes, J. Biomed. Nanotechnol. 10 (10) (2014) 2977–3003.
[69] P. Roy, S. Berger, P. Schmuki, TiO2 nanotubes: synthesis and applications, Angew. Chem. Int. Ed. 50 (13) (2011) 2904–2939.
[70] M.C. Turhan, R.P. Lynch, H. Jha, P. Schmuki, S. Virtanen, Anodic growth of self-ordered magnesium oxy-fluoride nanoporous/tubular layers on Mg alloy (WE43), Electrochem. Commun. 12 (6) (2010) 796–799.
[71] I. Degasne, M.F. Baslé, V. Demais, G. Huré, M. Lesourd, B. Grolleau, L. Mercier, D. Chappard, Effects of roughness, fibronectin and vitronectin on attachment, spreading, and proliferation of human osteoblast-like cells (Saos-2) on titanium surfaces, Calcif. Tissue Int. 64 (6) (1999) 499–507.
[72] M. Brust, M. Walker, D. Bethell, D.J. Schiffrin, R. Whyman, Synthesis of thiol-derivatised gold nanoparticles in a two-phase liquid–liquid system, J. Chem. Soc. Chem. Commun. (7) (1994) 801–802.
[73] T.-G. Iversen, T. Skotland, K. Sandvig, Endocytosis and intracellular transport of nanoparticles: present knowledge and need for future studies, Nano Today 6 (2) (2011) 176–185.
[74] N. Oh, J.-H. Park, Endocytosis and exocytosis of nanoparticles in mammalian cells, Int. J. Nanomed. 9 (Suppl 1) (2014) 51–63.
[75] A.G. Tkachenko, H. Xie, D. Coleman, W. Glomm, J. Ryan, M.F. Anderson, S. Franzen, D.L. Feldheim, Multifunctional gold nanoparticle-peptide complexes for nuclear targeting, J. Am. Chem. Soc. 125 (16) (2003) 4700–4701.
[76] N. Zhang, J. Lock, A. Sallee, H. Liu, Magnetic nanocomposite hydrogel for potential cartilage tissue engineering: synthesis, characterization, and cytocompatibility with bone marrow derived mesenchymal stem cells, ACS Appl. Mater. Interfaces 7 (37) (2015) 20987–20998.
[77] B.D. Chithrani, A.A. Ghazani, W.C. Chan, Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells, Nano Lett. 6 (4) (2006) 662–668.
[78] Y. Sun, Y. Xia, Shape-controlled synthesis of gold and silver nanoparticles, Science 298 (5601) (2002) 2176–2179.
[79] Y. Tan, X. Dai, Y. Li, D. Zhu, Preparation of gold, platinum, palladium and silver nanoparticles by the reduction of their salts with a weak reductant–potassium bitartrate, J. Mater. Chem. 13 (5) (2003) 1069–1075.
[80] Y. Sun, B.T. Mayers, Y. Xia, Template-engaged replacement reaction: a one-step approach to the large-scale synthesis of metal nanostructures with hollow interiors, Nano Lett. 2 (5) (2002) 481–485.
[81] P. Mukherjee, S. Senapati, D. Mandal, A. Ahmad, M.I. Khan, R. Kumar, M. Sastry, Extracellular synthesis of gold nanoparticles by the fungus Fusarium oxysporum, ChemBioChem 3 (5) (2002) 461–463.
[82] J.Y. Song, H.-K. Jang, B.S. Kim, Biological synthesis of gold nanoparticles using Magnolia kobus and Diopyros kaki leaf extracts, Process Biochem. 44 (10) (2009) 1133–1138.
[83] S.P. Chandran, M. Chaudhary, R. Pasricha, A. Ahmad, M. Sastry, Synthesis of gold nanotriangles and silver nanoparticles using Aloevera plant extract, Biotechnol. Prog. 22 (2) (2006) 577–583.
[84] Y.-h. Zheng, Y. Cheng, F. Bao, Y.-s. Wang, Synthesis and magnetic properties of Fe 3 O 4 nanoparticles, Mater. Res. Bull. 41 (3) (2006) 525–529.
[85] Z. Zhou, J. Wang, X. Liu, H. Chan, Synthesis of Fe3O4 nanoparticles from emulsions, J. Mater. Chem. 11 (6) (2001) 1704–1709.
[86] C.L. Wetteland, N.-Y.T. Nguyen, H. Liu, Concentration-dependent behaviors of bone marrow derived mesenchymal stem cells and infectious bacteria toward magnesium oxide nanoparticles, Acta Biomater. 35 (2016) 341–356.
[87] H. Mirzaei, A. Davoodnia, Microwave assisted sol-gel synthesis of MgO nanoparticles and their catalytic activity in the synthesis of hantzsch 1, 4-dihydropyridines, Chin. J. Catal. 33 (9) (2012) 1502–1507.
[88] P. Fedorov, E. Tkachenko, S. Kuznetsov, V. Voronov, S. Lavrishchev, Preparation of MgO nanoparticles, Inorg. Mater. 43 (5) (2007) 502–504.
[89] D.-M. Liu, T. Troczynski, W.J. Tseng, Water-based sol–gel synthesis of hydroxyapatite: process development, Biomaterials 22 (13) (2001) 1721–1730.
[90] Y. Wang, S. Zhang, K. Wei, N. Zhao, J. Chen, X. Wang, Hydrothermal synthesis of hydroxyapatite nanopowders using cationic surfactant as a template, Mater. Lett. 60 (12) (2006) 1484–1487.
[91] L.-y. Cao, C.-b. Zhang, J.-f. Huang, Synthesis of hydroxyapatite nanoparticles in ultrasonic precipitation, Ceram. Int. 31 (8) (2005) 1041–1044.

[92] Y. Sun, Y. Deng, Z. Ye, S. Liang, Z. Tang, S. Wei, Peptide decorated nano-hydroxyapatite with enhanced bioactivity and osteogenic differentiation via polydopamine coating, Colloids Surf. B Biointerfaces 111 (2013) 107–116.
[93] C. Qi, Y.J. Zhu, B.Q. Lu, X.Y. Zhao, J. Zhao, F. Chen, J. Wu, Hydroxyapatite hierarchically nanostructured porous hollow microspheres: rapid, sustainable microwave-hydrothermal synthesis by using creatine phosphate as an organic phosphorus source and application in drug delivery and protein adsorption, Chem. A Eur. J. 19 (17) (2013) 5332–5341.
[94] N.T. Thanh, L.A. Green, Functionalisation of nanoparticles for biomedical applications, Nano Today 5 (3) (2010) 213–230.
[95] L. Dykman, N. Khlebtsov, Gold nanoparticles in biomedical applications: recent advances and perspectives, Chem. Soc. Rev. 41 (6) (2012) 2256–2282.
[96] D.A. Giljohann, D.S. Seferos, W.L. Daniel, M.D. Massich, P.C. Patel, C.A. Mirkin, Gold nanoparticles for biology and medicine, Angew. Chem. Int. Ed. 49 (19) (2010) 3280–3294.
[97] S.D. Brown, P. Nativo, J.-A. Smith, D. Stirling, P.R. Edwards, B. Venugopal, D.J. Flint, J.A. Plumb, D. Graham, N.J. Wheate, Gold nanoparticles for the improved anticancer drug delivery of the active component of oxaliplatin, J. Am. Chem. Soc. 132 (13) (2010) 4678–4684.
[98] C.D. Medley, J.E. Smith, Z. Tang, Y. Wu, S. Bamrungsap, W. Tan, Gold nanoparticle-based colorimetric assay for the direct detection of cancerous cells, Anal. Chem. 80 (4) (2008) 1067–1072.
[99] M.A. Polizzi, N.A. Stasko, M.H. Schoenfisch, Water-soluble nitric oxide-releasing gold nanoparticles, Langmuir 23 (9) (2007) 4938–4943.
[100] H. Liu, T.J. Webster, Ceramic/polymer nanocomposites with tunable drug delivery capability at specific disease sites, J. Biomed. Mater. Res. Part A 93 (3) (2010) 1180–1192.
[101] L.J. Ignarro, Nitric oxide: a unique endogenous signaling molecule in vascular biology (Nobel lecture), Angew. Chem. Int. Ed. 38 (13–14) (1999) 1882–1892.
[102] B.M. Al Meslmani, G.F. Mahmoud, U. Bakowsky, Development of expanded polytetrafluoroethylene cardiovascular graft platform based on immobilization of poly lactic-co-glycolic acid nanoparticles using a wet chemical modification technique, Int. J. Pharm. 529 (1–2) (2017) 238–244.
[103] S. Ahadian, L.D. Huyer, M. Estili, B. Yee, N. Smith, Z.S. Xu, Y. Sun, M. Radisic, Moldable elastomeric polyester-carbon nanotube scaffolds for cardiac tissue engineering, Acta Biomater. 52 (2017) 81–91.
[104] M. Nahrendorf, F.A. Jaffer, K.A. Kelly, D.E. Sosnovik, E. Aikawa, P. Libby, R. Weissleder, Noninvasive vascular cell adhesion molecule-1 imaging identifies inflammatory activation of cells in atherosclerosis, Circulation 114 (14) (2006) 1504–1511.
[105] S. Kanno, Y.-J.L. Wu, P.C. Lee, S.J. Dodd, M. Williams, B.P. Griffith, C. Ho, Macrophage accumulation associated with rat cardiac allograft rejection detected by magnetic resonance imaging with ultrasmall superparamagnetic iron oxide particles, Circulation 104 (8) (2001) 934–938.
[106] C. Gruetter, B. Barry, D. McNamara, D. Gruetter, P. Kadowitz, L. Ignarro, Relaxation of bovine coronary artery and activation of coronary arterial guanylate cyclase by nitric oxide, nitroprusside and a carcinogenic nitrosoamine, J. Cycl. Nucleotide Res. 5 (3) (1978) 211–224.
[107] L. Ignarro, T. Burke, K. Wood, M. Wolin, P. Kadowitz, Association between cyclic GMP accumulation and acetylcholine-elicited relaxation of bovine intrapulmonary artery, J. Pharmacol. Exp. Ther. 228 (3) (1984) 682–690.
[108] C.A. Gruetter, D. Gruetter, J.E. Lyon, P.J. Kadowitz, L.J. Ignarro, Relationship between cyclic guanosine 3′: 5′-monophosphate formation and relaxation of coronary arterial smooth muscle by glyceryl trinitrate, nitroprusside, nitrite and nitric oxide: effects of methylene blue and methemoglobin, J. Pharmacol. Exp. Ther. 219 (1) (1981) 181–186.
[109] D.J. Smith, D. Chakravarthy, S. Pulfer, M.L. Simmons, J.A. Hrabie, M.L. Citro, J.E. Saavedra, K.M. Davies, T.C. Hutsell, D.L. Mooradian, Nitric oxide-releasing polymers containing the [N (O) NO]-group, J. Med. Chem. 39 (5) (1996) 1148–1156.
[110] J.R. McCarthy, F.A. Jaffer, R. Weissleder, A macrophage-targeted theranostic nanoparticle for biomedical applications, Small 2 (8–9) (2006) 983–987.
[111] H.D. Danenberg, I. Fishbein, J. Gao, J. Mönkkönen, R. Reich, I. Gati, E. Moerman, G. Golomb, Macrophage depletion by clodronate-containing liposomes reduces neointimal formation after balloon injury in rats and rabbits, Circulation 106 (5) (2002) 599–605.
[112] S. Shrivastava, T. Bera, S.K. Singh, G. Singh, P. Ramachandrarao, D. Dash, Characterization of antiplatelet properties of silver nanoparticles, ACS Nano 3 (6) (2009) 1357–1364.
[113] K. Chuang, K. Lee, C. Pan, C. Lai, L. Lin, S. Ho, K. Ho, H. Chuang, Effects of zinc oxide nanoparticles on human coronary artery endothelial cells, Food Chem. Toxicol. 93 (2016) 138–144.
[114] J. Roberts, R. Mercer, A. Stefaniak, M. Seehra, U. Geddam, I. Chaudhuri, A. Kyrlidis, V. Kodali, T. Sager, A. Kenyon, S. Bilgesu, T. Eye, J. Scabilloni, S. Leonard, N. Fix, D. Schwegler-Berry, B. Farris, M. Wolfarth, D. Porter, V. Castranova, A. Erdely, Evaluation of pulmonary and systemic toxicity following lung exposure to graphite nanoplates: a member of the graphene-based nanomaterial family, Part. Fibre Toxicol. 13 (2016).
[115] E. Smyth, A. Solomon, A. Vydyanath, P. Luther, S. Pitchford, T. Tetley, M. Emerson, Induction and enhancement of platelet aggregation in vitro and in vivo by model polystyrene nanoparticles, Nanotoxicology 9 (3) (2015) 356–364.
[116] M. Savi, S. Rossi, L. Bocchi, L. Gennaccaro, F. Cacciani, A. Perotti, D. Amidani, R. Alinovi, M. Goldoni, I. Aliatis, P. Lottici, D. Bersani, M. Campanini, S. Pinelli, M. Petyx, C. Frati, A. Gervasi, K. Urbanek, F. Quaini, A. Buschini, D. Stilli, C. Rivetti, E. Macchi, A. Mutti, M. Miragoli, M. Zaniboni, Titanium dioxide nanoparticles promote arrhythmias via a direct interaction with rat cardiac tissue, Part. Fibre Toxicol. 11 (2014).
[117] P. Danielsen, Y. Cao, M. Roursgaard, P. Moller, S. Loft, Endothelial cell activation, oxidative stress and inflammation induced by a panel of metal-based nanomaterials, Nanotoxicology 9 (7) (2015) 813–824.
[118] A. Nemmar, S. Beegam, P. Yuvaraju, J. Yasin, S. Tariq, S. Attoub, B.H. Ali, Ultrasmall superparamagnetic iron oxide nanoparticles acutely promote thrombosis and cardiac oxidative stress and DNA damage in mice, Part. Fibre Toxicol. 13 (2016) 11.
[119] Z.L. Sun, L.Y. Yang, K.F. Chen, G.W. Chen, Y.P. Peng, J.K. Chen, G.L. Suo, J.T. Yu, W.C. Wang, C.H. Lin, Nano zerovalent iron particles induce pulmonary and cardiovascular toxicity in an in vitro human co-culture model, Nanotoxicology 10 (7) (2016) 881–890.
[120] J. Guo, T. Shi, X. Cui, Y. Rong, T. Zhou, Z. Zhang, Y. Liu, Y. Shen, W. Chen, Effects of silica exposure on the cardiac and renal inflammatory and fibrotic response and the antagonistic role of interleukin-1 beta in C57BL/6 mice, Arch. Toxicol. 90 (2) (2016) 247–258.
[121] Z. Chen, Y. Wang, L. Zhuo, S. Chen, L. Zhao, X. Luan, H. Wang, G. Jia, Effect of titanium dioxide nanoparticles on the cardiovascular system after oral administration, Toxicol. Lett. 239 (2) (2015) 123–130.
[122] B. Kang, M.A. Mackey, M.A. El-Sayed, Nuclear targeting of gold nanoparticles in cancer cells induces DNA damage, causing cytokinesis arrest and apoptosis, J. Am. Chem. Soc. 132 (5) (2010) 1517–1519.
[123] C. Bussy, L. Methven, K. Kostarelos, Hemotoxicity of carbon nanotubes, Adv. Drug Deliv. Rev. 65 (15) (2013) 2127–2134.
[124] S.J. Evani, A.K. Ramasubramanian, Hemocompatibility of Nanoparticles, Nanobiomaterials Handbook, CRC Press, 2011, pp. 1–17.
[125] S. Franz, S. Rammelt, D. Scharnweber, J.C. Simon, Immune responses to implants–a review of the implications for the design of immunomodulatory biomaterials, Biomaterials 32 (28) (2011) 6692–6709.
[126] J.M. Anderson, A. Rodriguez, D.T. Chang, Foreign Body Reaction to Biomaterials, Seminars in Immunology, Elsevier, 2008, pp. 86–100.
[127] F. Velard, J. Braux, J. Amedee, P. Laquerriere, Inflammatory cell response to calcium phosphate biomaterial particles: an overview, Acta Biomater. 9 (2) (2013) 4956–4963.
[128] F. Boccafoschi, C. Mosca, M. Cannas, Cardiovascular biomaterials: when the inflammatory response helps to efficiently restore tissue functionality? J. Tissue Eng. Regen. Med. 8 (4) (2014) 253–267.
[129] H. Liu, T.J. Webster, Enhanced biological and mechanical properties of well-dispersed nanophase ceramics in polymer composites: from 2D to 3D printed structures, Mater. Sci. Eng. C 31 (2) (2011) 77–89.
[130] I. Johnson, K. Akari, H. Liu, Nanostructured hydroxyapatite/poly (lactic-co-glycolic acid) composite coating for controlling magnesium degradation in simulated body fluid, Nanotechnology 24 (37) (2013), 375103.
[131] Q. Tian, H. Liu, Electrophoretic deposition and characterization of nano-composites and nanoparticles on magnesium substrates, Nanotechnology 26 (17) (2015) 175102.
[132] Q. Tian, L. Rivera-Castaneda, H. Liu, Optimization of nano-hydroxyapatite/poly (lactic-co-glycolic acid) coatings on magnesium substrates using one-step electrophoretic deposition, Mater. Lett. 186 (2017) 12–16.
[133] H. Ghanbari, H. Viatge, A.G. Kidane, G. Burriesci, M. Tavakoli, A.M. Seifalian, Polymeric heart valves: new materials, emerging hopes, Trends Biotechnol. 27 (6) (2009) 359–367.
[134] J.A. Rogers, K.E. Paul, R.J. Jackman, G.M. Whitesides, Using an elastomeric phase mask for sub-100 nm photolithography in the optical near field, Appl. Phys. Lett. 70 (20) (1997) 2658–2660.
[135] H.E. Jeong, S.H. Lee, P. Kim, K.Y. Suh, Stretched polymer nanohairs by nanodrawing, Nano Lett. 6 (7) (2006) 1508–1513.
[136] M. Shevach, B. Maoz, R. Feiner, A. Shapira, T. Dvir, Nanoengineering gold particle composite fibers for cardiac tissue engineering, J. Mater. Chem. B 1 (39) (2013) 5210–5217.
[137] M.M. Kemp, A. Kumar, S. Mousa, T.-J. Park, P. Ajayan, N. Kubotera, S.A. Mousa, R.J. Linhardt, Synthesis of gold and silver nanoparticles stabilized with glycosaminoglycans having distinctive biological activities, Biomacromolecules 10 (3) (2009) 589–595.
[138] G. Frens, Controlled nucleation for the regulation of the particle size in monodisperse gold suspensions, Nature 241 (105) (1973) 20–22.
[139] N.C. Bigall, T. Härtling, M. Klose, P. Simon, L.M. Eng, A. Eychmüller, Monodisperse platinum nanospheres with adjustable diameters from 10 to 100 nm: synthesis and distinct optical properties, Nano Lett. 8 (12) (2008) 4588–4592.
[140] L. Zhang, L. Laug, W. Munchgesang, E. Pippel, U. Gösele, M. Brandsch, M. Knez, Reducing stress on cells with apoferritin-encapsulated platinum nanoparticles, Nano Lett. 10 (1) (2009) 219–223.
[141] W. He, X. Liu, A. Kienzle, W. Muller, Q. Feng, In vitro uptake of silver nanoparticles and their toxicity in human mesenchymal stem cells derived from bone marrow, J. Nanosci. Nanotechnol. 16 (1) (2016) 219–228.
[142] W. Rieter, K. Pott, K. Taylor, W. Lin, Nanoscale coordination polymers for platinum-based anticancer drug delivery, J. Am. Chem. Soc. 130 (35) (2008) 11584.
[143] A.H. Lu, E.e.L. Salabas, F. Schüth, Magnetic nanoparticles: synthesis, protection, functionalization, and application, Angew. Chem. Int. Ed. 46 (8) (2007)

1222–1244.
[144] J. Weizenecker, B. Gleich, J. Rahmer, H. Dahnke, J. Borgert, Three-dimensional real-time in vivo magnetic particle imaging, Phys. Med. Biol. 54 (5) (2009) L1–L10.
[145] S. Ahadian, S. Yamada, J. Ramon-Azcon, M. Estili, X.B. Liang, K. Nakajima, H. Shiku, A. Khademhosseini, T. Matsue, Hybrid hydrogel-aligned carbon nanotube scaffolds to enhance cardiac differentiation of embryoid bodies, Acta Biomater. 31 (2016) 134–143.
[146] T. Dvir, M. Bauer, A. Schroeder, J.H. Tsui, D.G. Anderson, R. Langer, R. Liao, D.S. Kohane, Nanoparticles targeting the infarcted heart, Nano Lett. 11 (10) (2011) 4411–4414.
[147] K.S. Oh, J.Y. Song, S.J. Yoon, Y. Park, D. Kim, S.H. Yuk, Temperature-induced gel formation of core/shell nanoparticles for the regeneration of ischemic heart, J. Control. Release 146 (2) (2010) 207–211.
[148] I.C. Turnbull, A.A. Eltoukhy, K.M. Fish, M. Nonnenmacher, K. Ishikawa, J.Q. Chen, R.J. Hajjar, D.G. Anderson, K.D. Costa, Myocardial delivery of lipidoid nanoparticle carrying modRNA induces rapid and transient expression, Mol. Ther. 24 (1) (2016) 66–75.